AN ABSTRACT OF THE THESIS OF

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Title: A STUDY OF THE PERMANGANATE OXIDATION OF 4-METHYLPYRIMIDINE TO PYRIMIDINE 4-CARBOXYLIC ACID

Abstract approved: Redacted for Privacy
Professor Bert E. Christensen

The yields from the oxidation of 4-methylpyrimidine with potassium permanganate were found to increase from 25 to 92 percent by the addition of small amount of potassium hydroxide to the reaction mixture.

Pyrimidine-4-carboxylic acid decarboxylates in hot aqueous solution to yield pyrimidine and carbon dioxide. The rate is that decarboxylation is markedly effected by the alkalinity of the solution. No unreacted 4-methylpyrimidine survived the permanganate oxidation as reported by Gabriel.

Several derivatives of pyrimidine-4-carboxylic acid were prepared.

The pyrimidine-4-carboxylic acid was found to be water

soluble only to the extent of one part in 300 at room temperature but fairly soluble at elevated temperature. The ionization constant of the acid was found to be 6.1×10^{-4}.

4-Methylpyrimidine is best prepared by the one-step operation involving the condensation of 4, 4-dimethyoxy-2-butanone and formamide as reported by Bredereck, Gompper and Morlock.

2, 6-Dichlo-4-methylpyrimidine was found to be so unstable as to be unsuitable for synthetic work even when at deepfreeze temperatures over period of several days.

A Study of the Permanganate Oxidation of 4-Methylpyrimidine to Pyrimidine-4-carboxylic Acid

by

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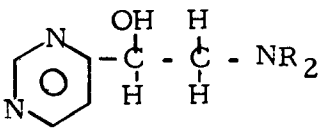
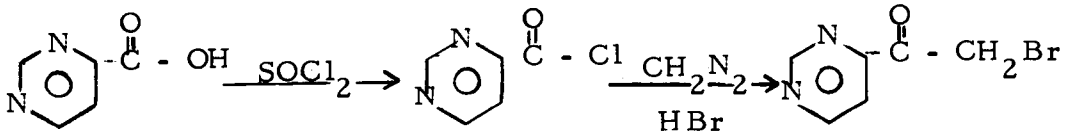
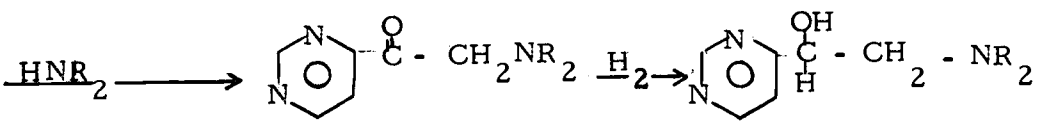
INTRODUCTION

One of the sought after compounds in the anti-malarial program (6) was an aminoalcohol having a structure similar to quinine but replacing the quinoline and quinuclidine moiety with a pyrimidine and an alkylamine base e.g.



The proposed sequence of reactions for the synthesis of this potential drug was as follows:





In recent years pyrimidine-4-carboxylic acid and some of its derivatives have been reported as having certain desirable biological properties (5, 9). For example it has been discovered that the hydrazide of pyrimidine-4-carboxylic acid is a potential anti-tuberculosis agent (9).

Furthermore the acid itself has demonstrated significant cardiac effects in the isolated hearts taken from dogs (5).

The bottleneck to the development of these drugs stems from the difficulty of preparing the pyrimidine-4- or pyrimidine-5-carboxylic acids in sufficient amounts to meet the demands of such investigations.

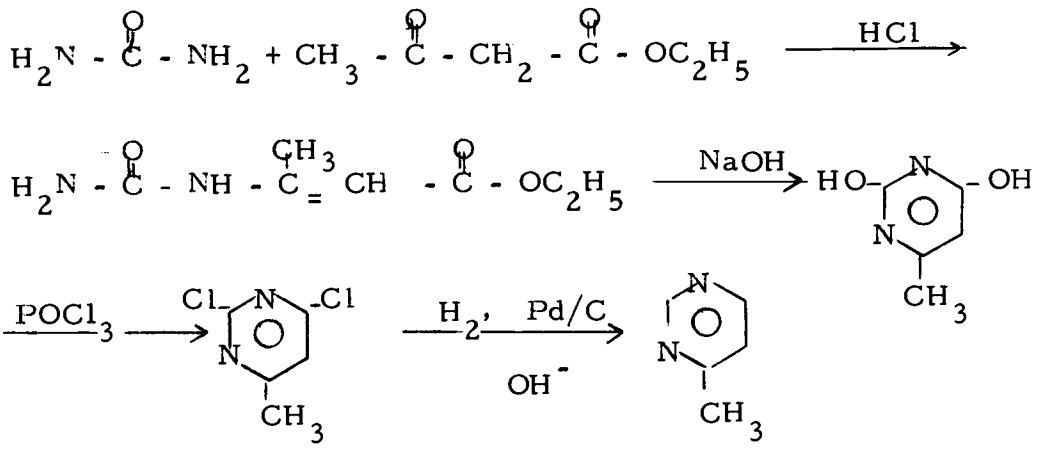
These key intermediates have been prepared in very poor yield by potassium permanganate oxidation of the respective methyl-pyrimidines which has seriously restricted the use of this acid for investigative purposes. Because of the renewed interest in pyrimi dine acids as starting materials for potential pyrimidine drugs this study was undertaken.

The starting material for this investigation was ethyl aceto-acetate which was condensed under acidic conditions with urea according to the directions of Donleavy and Kiss (7) to yield the ureide $H_2N-\overset{O}{\overset{\|}{C}}-\overset{H}{\overset{|}{N}}-\overset{CH_3}{\overset{|}{C}}=CH-\overset{O}{\overset{\|}{C}}-OR$. This intermediate in turn cyclized, when placed in a strong basic solution to yield 4-methyluracil in good yield.

The treatment of 4-methyluracil with phosphorus oxychloride according to the directions of Gabriel (8) gave the corresponding 2,6-dichloro-4-methylpyrimidine.

The catalylic reduction of the 2,6-dichloro-4-methylpyrimidine

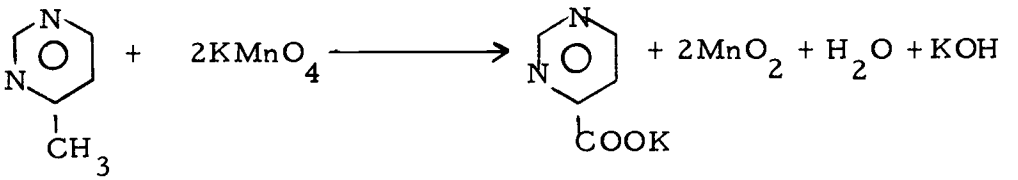
according to the procedure of Smith and Christensen (12) gave 4-methylpyrimidine in reasonable yields.



Two other procedures yielding 4-methylpyrimidine by a one-step condensation have been reported. Bredereck, Gompper and Morlock (4) have prepared it by condensation of 4, 4-dimethoxy-2-butanone and formamide in 50-60 percent yield. Bredereck, Gompper and Geiger (3) also have prepared it from trisformylaminomethane and acetone in 39 percent yield. Both of these methods have been studies in this laboratory and the former method was found to be much simpler and gave better yields. 4, 4-Dimethoxy-2-butanone being a relatively cheap commercially available intermediate makes this one step procedure very attractive for the preparation of 4-methyl-pyrimidine.

Pyrimidine-4-carboxylic acid has been prepared by the permanganate oxidation as early as 1899 (8). The process involves the oxidation of 4-methylpyrimidine over a six hours period in a dilute

aqueous solution using the theoretical amount of oxidant to convert it to the corresponding acid according to the reaction



The yields in this final step are low, averaging around 25 percent. It has been reported by Gabriel (8) that under these conditions that not all of the 4-methylpyrimidine is oxidized. Approximately 20 percent of the unreacted starting material being recovered from the distillate obtained during the concentration of the final reaction media. The potassium salt of the pyrimidine-4-carboxylic acid remaining in the concentrate, is liberated as the free acid by treatment with a stoichemitrical quantity of concentrated nitric acid.

This distillate obtained from the concentration of pyrimidine-4-carboxylic acid is treated with mercuric chloride which complexes with the unreacted 4-methylpyrimidine can be recovered by treatment with hydrated sodium sulfide (10).

Pyrimidine mercuric chloride complex + $Na_2S \cdot 9\ H_2O \longrightarrow$ 4-methylpyrimidine + HgS + 2NaCl

To effect the isolation of the potassium salt of pyrimidine-4-carboxylic the final reaction mixture is filtered to remove the insoluble manganese dioxide and then concentrated by vacuum distillation until the total solid content is approximately ten percent. The

free acid is then precipitated by the addition of concentrated nitric acid in an amount just sufficient to convert all potassium ion to the nitrate salt while taking precautions to keep sufficient solvent available to prevent any precipitation of potassium nitrate. The pyrimidine-4-carboxylic acid is then filtered and washed by resuspending it in about five parts of cold water to assure the removal of any inorganic contaminants.

DISCUSSION AND RESULTS

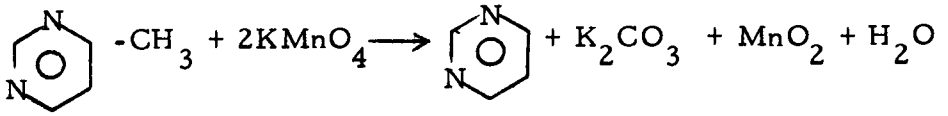
The oxidation under the above conditions leaves approximately 50 percent of the original starting material 4-methylpyrimidine unaccounted for. Since recovery of manganese dioxide is approximately theoretical, there does not appear to be any coprecipitation of the product with manganese dioxide. Since the potassium permanganate was just sufficient to effect the conversion of the 4-methylpyrimidine to the corresponding acid, the low yields can only be attributed to (a) oxidation resulting in the fragmentation of the nucleus while leaving some of the original 4-methylpyrimidine intact or (b) gradual decarboxylation of the pyrimidine-4-carboxylic acid product during the oxidation to yield pyrimidine which would also have been precipitated as a mercury complex (10) along with any unreacted 4-methylpyrimidine from the distillate of the final reaction mixture.

Should the reaction proceed by either pathway there would be a build-up of carbon dioxide in the reaction media. This is found to be the case and this carbon dioxide is released by the nitric acid prior to the precipitation of the pyrimidine-4-carboxylic acid from the concentrate of the final reaction mixture.

The reaction media for the conversion of 4-methylpyrimidine to the corresponding acid consists of dilute aqueous solution of 4-methylpyrimidine to which a theoretical quantity of dilute

permanganate solution was added over a period of several hours. If 4-methylpyrimidine is recovered from the distillate obtained from the concentration of the potassium pyrimidine-4-carboxylate as reported by Gabriel (8) then the low yields can only be attributed to fragmentation of the pyrimidine ring through further oxidation.

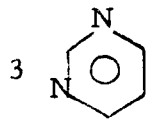
Thus the measurement of this carbon dioxide might provide some evidence as to the pathway of this reaction, and for this reason aliquots from the final oxidation media were titrated with standard acid to determine the bicarbonate content. If the reaction responsible for carbon dioxide production proceeded to pyrimidine (rather than the acid)



one obtains a half mole of potassium carbonate per mole of potassium permanganate consumed. Thus one might obtain an estimate of the carbon dioxide produced from that part of the titration curve typical of the bicarbonate ion behavior, the initial part of the curve would measure the total alkaline content due to any free potassium hydroxide and potassium carbonate. However, the buffering effect of the potassium pyrimidine-4-carboxylic would probably make an accurate estimation of the bicarbonate ion impossible.

The aliquot from an experiment in which the yield of pyrimidine-4-carboxylic acid was 25 percent gave a value of 70

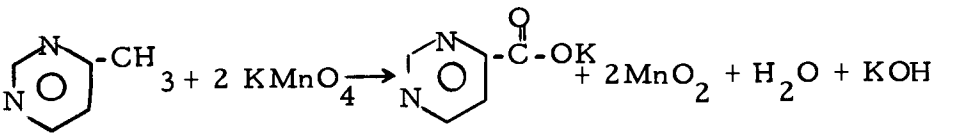
percent for the carbon dioxide formation (calculated on the basis of one mole of carbon dioxide produced per mole 4-pyrimidine oxidized). In a later experiment in which the yield of pyrimidine-4-carboxylic acid was 77 percent a value of 23.4 percent was obtained for the carbon dioxide evolved. If some of the pyrimidine ring is fragmented through oxidation one would have expected a greater amount of carbon dioxide to have been produced per mole oxident consumed



$$3 \; + \; CH_3 \; + 20\ KMnO_4 + 10\ H_2O \longrightarrow 15\ KHCO_3 + 6\ NH_3$$

$$+ 20\ MnO_2 + 5KOH$$

while leaving a considerably reduced amount of potassium permanganate as indicated in above equation to account for the conversion of 4-methylpyrimidine to the corresponding acid. Such behavior would account for the unreacted 4-methylpyrimidine recovered from the reaction product as reported by Gabriel (8). The reaction responsible for the acid proceeds as



The reaction medium is approximately neutral in the initial stages and proceeds to become more alkaline as the reaction progresses. If the low yields stem from decarboxylation of the acid, the pH of the solution should have a marked affect on the stability of the acid. It would appear more probable that any decarboxylation

would occur at the initial stages of the reaction and not at a time when the build up of the alkaline content become appreciable.

For these reasons experiments were initiated in this study in which the reaction mixture was altered by the addition of varying amounts of potassium hydroxide to the reaction mixture. Since the final isolation of the product, pyrimidine-4-carboxylic acid depends on its separation from potassium nitrate, the amount of base that can be added to the reaction medium is limited. From this study it was quite apparent that the pH of the solution did have a profound effect on the yield of pyrimidine-4-carboxylic acid. When the alkalinity of the initial reaction media was made 0.16 N with respect to potassium hydroxide the yield rose from 25 to 92 percent.

If the low yield of the oxidative step stemmed from decarboxylation of the pyrimidine-4-carboxylic acid then one should recover pyrimidine free base from the aqueous reaction media. Upon the concentration of solutions of potassium pyrimidine-4-carboxylate from the oxidation of 4-methylpyrimidine, the distillate was treated with mercuric chloride to recover the pyrimidine bases as their insoluble mercuric chloride complexes (8, 10). The mercuric complexes were treated with hydrated sodium sulfide using distillation techniques. The volatile bases were recovered as aqueous soltuions from which they were isolated by ether extration. The pyrimidine fraction was then examined by gas chromatography.

These experiments indicated that the free pyrimidine base fraction consisted entirely of pyrimidine; there was no evidence of any 4-methylpyrimidine. Thus the carbon dioxide liberated during the reaction came from the decarboxylation on the pyrimidine-4-carboxylate and not from the further oxidation of the acid. Gabriel (8) was in error when he reported 4-methypyrimidine in the distillate from the permanganate oxidation as there is no evidence to support further oxidation of the pyrimidine ring.

Pyrimidine-4-carboxylic acid is readily converted to the acid chloride using thionyl chloride. The acid chloride in turn can be used to make a number of derivatives including the amide, hydrazide and ester.

The acid chloride reacts with diazomethane to yield 4-diazoacetylpyrimidine which when treated according to directions of Siegle and Christensen (11) with hydrobromic acid yield 4-bromoacetylpyrimidine which is a useful intermediate for the preparation of potential anti-malarials.

Pyrimidine-4-carboxylic acid is only slightly soluble in cold water to the extent of approximately one part in three hundred. It is fairly soluble in hot water, thus water is a good crystallizing solvent for this material.

Because of the low water solubility of pyrimidine-4-carboxylic acid the ionization constant was determined from spectral

transmission data according to the method of Stenstrom and Reinhard (13).

This procedure was based on the assumption that for certain compounds two forms of absorbing species existed, one is an acidic medium and the other in a basic medium, each of which is capable of yielding its own absorption curve in the ultraviolet. Thus at a given wave length there should be a significant difference between the extinction coefficients of the two structures taken at a fixed pH. It was also assumed that a mixture of the two types of absorbing units coexisting at a given pH would have an extinction coefficient lying between those two values and that the relationship between them would be: $x(1-a) + ya = E$

where a = fraction of the molecule ionized at the carboxyl group.

1 - a = extinction coefficient of molecule not ionized at the carboxyl group.

x = extinction coefficient of molecules not ionized at the carboxyl group.

y = extinction coefficient of molecule ionized at the carboxyl group.

E = extinction coefficient of a mixture of the two species

c = original concentration

Ka = dissociation constant

Since $[H^+] \times [\text{anion}^-] = Ka \times [\text{acid}]$

$$[H^+] \times a\,c = Ka \times c\,(1 - a)$$

where $$a = \frac{Ka}{[H^+] + Ka}$$

and $$E = x\left[\frac{[H^+]}{[H^+] + Ka}\right] + y\left[\frac{Ka}{[H^+] + Ka}\right]$$

and $$Ka = \frac{(E - x)}{(y - E)} \times [H^+]$$

The dissociation constant can be calculated when x and y are known and the value of E lying between x and y have been determined for a given pH. Using this procedure the Ka of pyrimidine-4-carboxylic acid was found to be 6.1×10^{-4}.

EXPERIMENTAL

4-Methyluracil

To a mixture consisting of 80 g (1.33 moles) of finely powder urea and 160 g (1.23 moles) of ethyl acetoacetate in five inch crystallizing dish is added 25 ml of absolute alcohol and ten drops of concentrated hydrochloric acid. The mixture is then well stirred and then covered with a watch glass and placed in a vacuum desiccator using concentrated sulfuric acid as the dessicant. The desiccator is evacuated with a water aspirator intermittantly over a period of several days until the mixture appears to be bone dry. The yield of crude β-uraminocrotonic ethyl ester is 200 grams.

To a hot solution (95°C) consisting of 80 g (2 moles) of sodium hydroxide in 1.2 liter of water is added with careful stirring 200 g of ethyl β-uraminocrotonate. After cooling the clear solution to 65°C it is carefully stirred and acidified by the slow addition of 160 ml of concentrated hydrochloric acid, which precipitates the 4-methyluracil. After the mixture has cooled, the product is removed by filtration, washed in turn with cold water, alcohol and ether and then air dried. Yield 110 g (70 percent), m. p. above 300°C .

2, 6-Dichloro-4-methylpyrimidine

A mixture consisting of 50 g of 4-methyluracil and 200 ml of phosphorus oxychloride is refluxed for five hours. The methyluracil gradually goes into solution with a evolution of hydrogen chloride yielding a dark homogeneous solution. The excess phosphorus oxychloride is then removed by vacuum distillation with a water aspirator and the resultant viscous residue is added gradually to 500 g of crushed ice. This mixture is immediately extracted with one liter of ether. The ethereal extracts are washed with ten percent sodium carbonate solution and finally dried over anhydrous magnesium sulfate. Removal of the ether by distillation leaves the 2, 6-dichloro-4-methylpyrimidine which was isolated by vacuum distillation to yield a solid product. Yield 51 g (78 percent), m. p. 47 ^{o}C . This material was found to be somewhat unstable and should be used immediately otherwise one obtains low yield on reduction to 4-methylpyrimidine.

2, 4-Dichloro-4-methylpyrimidine was found to be unstable even when stored at deepfreeze temperatures. After storage for a period of two weeks at these low temperatures the compound was almost completely altered as judged by melting point data.

4-Methylpyrimidine

Method A

A mixture consisting of 8.1 g of freshly prepared 2, 6-dichloro-4-methylpyrimidine (0.05 moles) in 100 ml of ether is added to 20 ml of water containing 0.5 g of ten percent palladized charcoal and five g of sodium hydroxide pellets. The resultant mixture was shaken with hydrogen at an initial pressure of three atmospheres (45 lbs/sq inch) until hydrogen absorption ceased (three hours). The catalyst is then removed by filtration and washed with two five ml portion of hot water. The ether is then separated and the aqueous portion together with wash water is continuously extracted with fresh ether for 24 hours. The ether fractions are combined and then dried over anhydrous magnesium sulfate. The dried ethereal solution is then distilled in a simple distillation apparatus to remove the ether and the residue then is distilled in a good fractionation column (e. g. Podbielniak column). Yield of 4-methylpyrimidine 3.6 g (78 percent), B. P. 141°C.

Method B

Trisformylaminomethane

Dimethyl sulfate (63 g) and formamide (225 g) are heated in a

vacuum distillation apparatus for 1.5 hours at 80° at 15-18 mm pressure (water aspirator). After cooling the reaction mixture was placed in deepfreeze for 48 nours. Trisformylaminomethane (21 g) crystallizes out from the clear syrupy solution, m.p. 168-170° C. Concentration of the mother solution recover an additional 22.3 g gave total yield 43.3 g (60 percent). The product obtained in this manner is sufficiently pure for the next step of the preparation.

4-Methylpyrimidine

Acetone (29 g), trisformylaminomethane (36 g), formamide (30 ml) and p-toluenesulfonic acid (0.5 g) are slowly heated to 155° C in the autoclave with shaking. The reaction mixture is maintained at this temperature for ten hours, on cooling, it is treated with 500 ml of 1N NaOH solution and aqueous solution extracted several times with small portions of chloroform. Drying of the chloroform extracts over sodium sulfate and fractional distillation using a Podbielniak column afford the product, B.P. 141°C, yield 6.8 g (25 percent).

Method C

Formamide (150 ml), water (5 ml), and ammomium chloride (10 g) is charged in a 500 ml of three necked flask which is equipped with a stirrer, a thermometer, a separatory funnel and a Liebig reflux condenser. A second Liebig condenser set downward for

distillation is connected to the top of the reflux condenser by means of a head provided with a thermometer well. The mixture is heated to 183°C in a thermowell, and 80 g of 4, 4-dimethoxy-2-butanone is added dropwise with stirring over six hours. The flow of cooling water in the reflux condenser should be adjusted to a rate such that the methanol and methyl formate formed during the reaction distill out. After all the acetal has been added, heating is continued for one hour, and the cooled reaction mixture poured into 200 ml of 1N sodium hydroxide solution. The resultant solution is extracted with chloroform in a liquid-liquid extractor for 24 hours. The chloroform is separated, dried over sodium sulfate, and removed by distillation. The dark-colored residue is distilled through a Podbielniak column at atmospheric pressure, B. P. 141°C , yield 20. 6 g (33 percent).

Pyrimidine-4-carboxylic acid

Six grams of 4-methylpyrimidine is dissolved in 600 ml of water and placed in three necked flask equipped with glass-co mantle, stirrer, condenser and dropping funnel. The solution is brought to a gentle reflux and 1200 ml of a dilute solution containing 20. 2 g of potassium permanganate are added dropwise over a period of four hours. The solution is heated for an additional two hours and then left overnight.

The manganese dioxide is then removed from the colorless

solution by filtration and washed with 100 ml of water. The combined aqueous fractions are then concentrated by vacuum distillation to approximately 300 ml refiltered to remove final traces MnO_2. The clear concentrate was then placed in a rototary evaporator and concentrated to approximately 50 ml. The distillate from the initial concentration was saved and pyrimidine bases were recovered as mercuric chloride complexes. To this final concentrate was carefully added eight g of 70 percent (1.42 density) concentrated nitric acid just sufficient to convert all the potassium hydroxide and (or) potassium carbonate to potassium nitrate. This precipitates the pyrimidine-4-carboxylic acid as a white powder. After standing for two hours the product is removed by filtration, then resuspended in 25 ml cold water, stirred, filtered and washed with 10 ml of ice water. Yield about 2.0 g, m.p. 236°C (dec.).

This procedure was modified by making the original 4-methylpyrimidine solution more basic with additional potassium hydroxide, and adjusting the amounts of nitric acid to remove all the additional potassium ion as the corresponding nitrate salts. The results of the experiments are given in Table I.

Recovery of pyrimidine bases

The distillate from concentration of the oxidation product was treated with two percent mercuric chloride to precipitate any

TABLE I.

Experiment	Grams of additional KOH/run	Percent Yield
1	--	26.0
2	--	25.0
3	0.168	44.0
4	0.336	57.0
5	0.336	39.2
6	0.672	83.5
7	1.344	77.0
8	2.688	81.0
9	2.688	86.0
10	5.376	92.5
11	5.376	92.0
12	10.752	90.0
13	10.752	89.8

pyrimidine or 4-methlypyrimidine as mercuric chloride complex (8, 10). These precipitates (from several runs) were washed and dried.

Eleven grams of the mercuric chloride-pyrimidine base complexes were distilled with 11.5 grams of sodium sulfide hydrate ($Na_2S \cdot 9\ H_2O$) and the distillate saturated with potassium carbonate. This gave two layers (upper pyrimidine fraction, lower aqueous fraction).

The aqueous fraction was extracted three times with ether. The extract was combined with upper layer and the resultant ethereal solution was dried over anhydrous calcium sulfate. After removal of the drying agent by filtration, the ethereal solution was examined in a gas chromatographic apparatus. The ether solution contained two components which were identified as ether and pyrimidine. The results of these experiments are illustrated in Figure 1 and 2. No 4-methylpyrimidine was observed. Thus carbon dioxide can only be accounted for as a consequence of the decarboxylation of pyrimidine-4-carboxylic acid.

Preparation of pyrimidine-4-carbamide

One gram of pyrimidine-4-carboxylic acid was heated under reflux with five ml of thionyl chloride for 30 minutes, and the excess removed by distillation. The reaction mixture was then allowed to cool and gradually poured into 15 ml of concentrated ammonium hydroxide solution with vigorous stirring. After standing 24 hours, the precipitate was collected on a filter and purified by recrystallization from 75 percent ethyl alcohol. Recovery of a second crop of crystals from mother liquors provided a total yield of 700 mg (70 percent). M. p. of amide was over 300^{o}C.

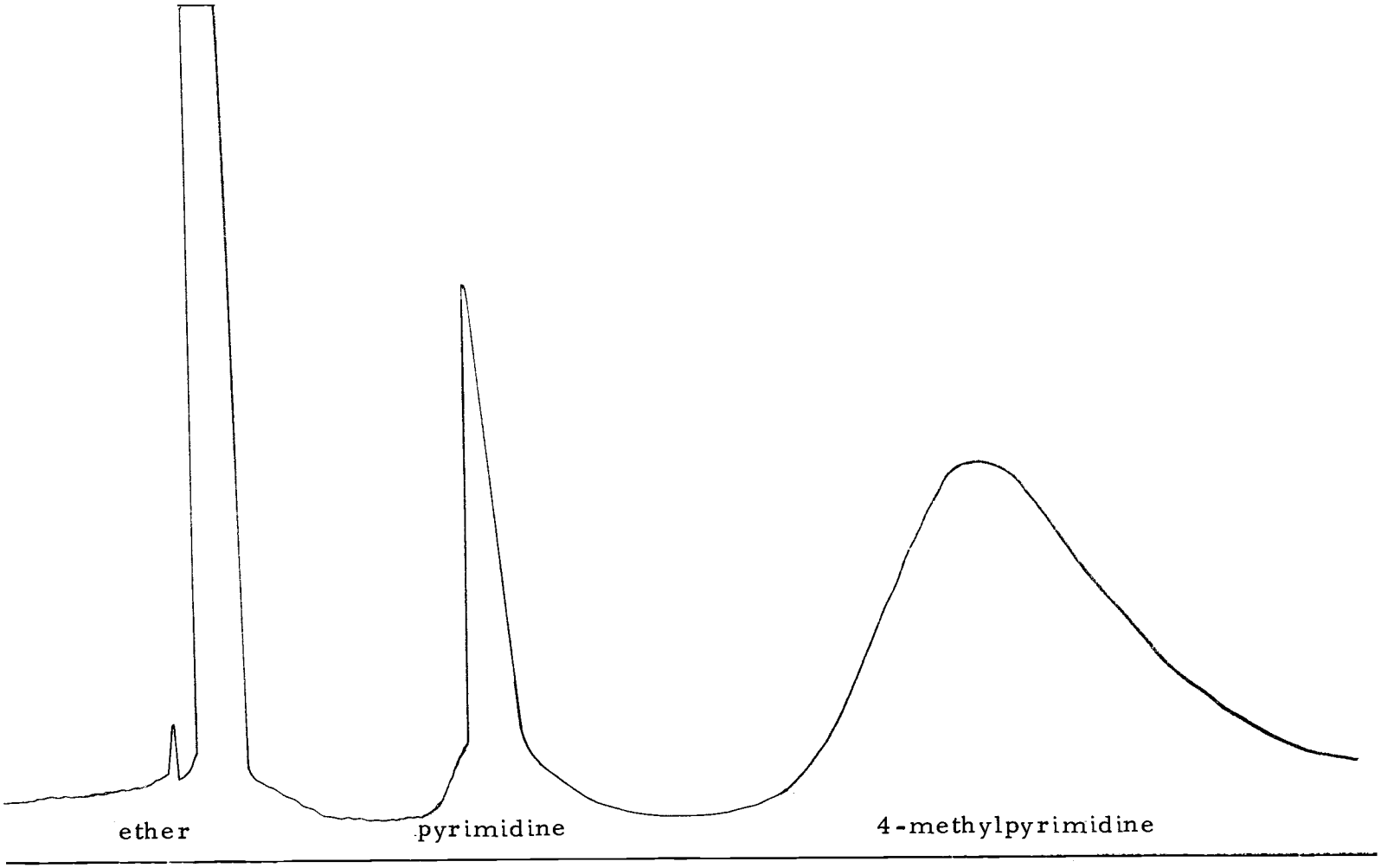


Figure 1. G. L. C. of a mixture of ether, 4-methylpyrimidine and pyrimidine.

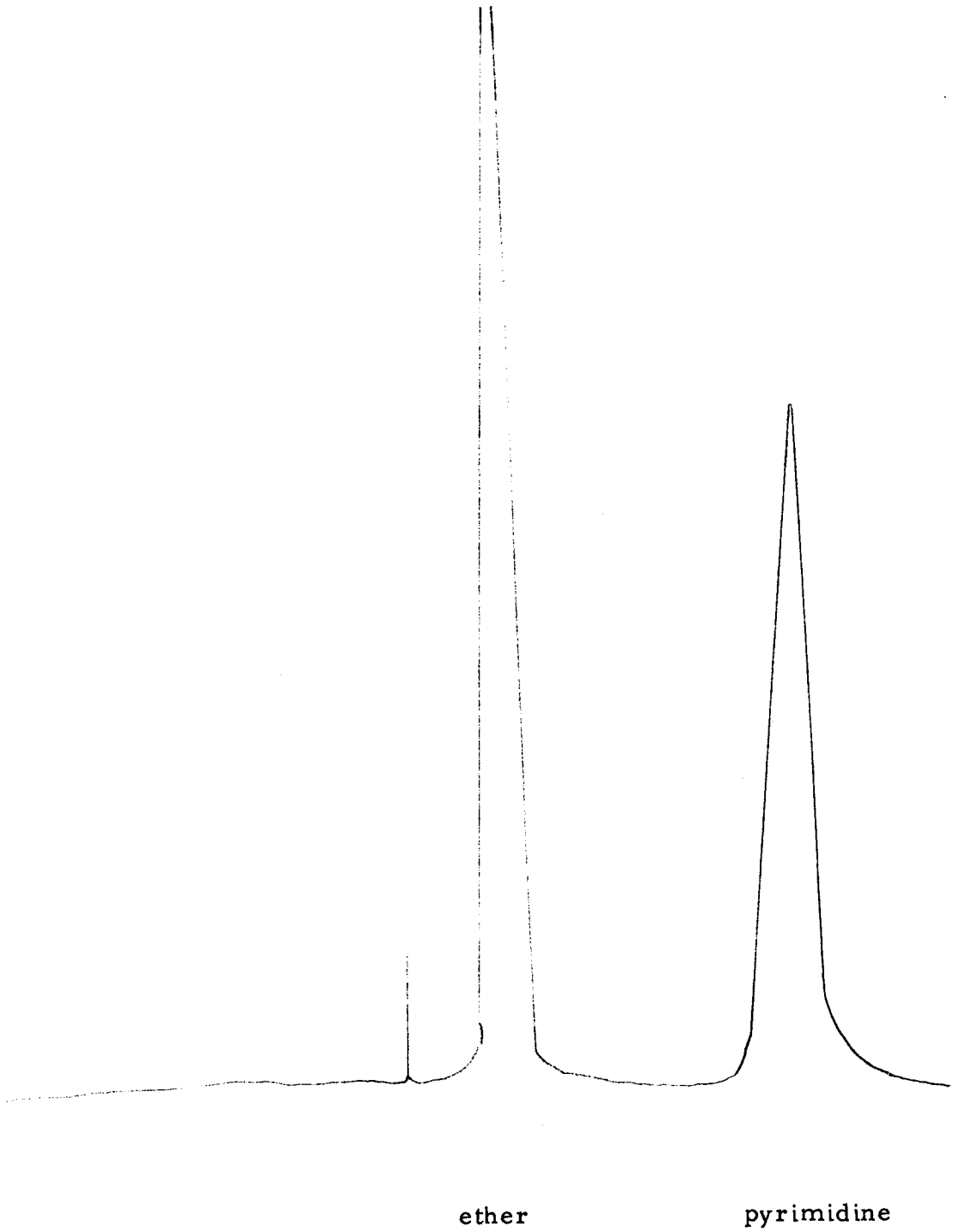


Figure 2. G. L. C. of pyrimidine fraction recovered from distillate obtained on concentration of pyrimidine-4-carboxylic acid.

Preparation of 4-bromoacetylpyrimidine

Nitrosomethylurea (1)

A solution of 100 grams of methylamine hydrochloride and 300 grams of urea in 400 ml of distilled water is boiled gently under reflux for three hours and then vigorously for 15 minutes. The solution is cooled to room temperature and 110 grams of sodium nitrite is dissolved in it, and the whole is cooled to about -10° C and then added slowly with vigorous stirring to a mixture of 600 grams of ice and 110 grams of concentrated sulfuric acid cooled in an ice salt bath. The nitrosomethylurea immediately separates as a crystalline precipitate, which is collected on a filter, washed with cold water, and dried in a vacuum desiccator to constant weight. Yield 115 grams.

Diazomethane (2)

To 32 ml of dry ether is added 9.8 ml 40 percent potassium hydroxide were stirred in a 125 ml Erlenmeyer flask which was cooled with dry-ice-acetone bath. To this, with continued cooling and shaking was added 3.2 grams finely powdered nitrosomethylurea in small portions over a period of two minutes. After solution was completed the deep yellow ethereal layer was separated and dried over potassium hydroxide pellets for four hours for use in next step of the preparation.

4-Bromoacetylpyrimidine

The acid chloride prepared in the preceding operation was diluted with 20 ml dry ether and then added dropwise to the diazomethane solution. After four hours 20 ml of ether was added and then five ml of 48 percent hydrobromic acid was added dropwise with stirring. The ethereal solution separated into two layers. The aqueous layer was extracted three times with 20 ml of ether. The fractions were combined and ether removed leaving a yellow-orange residue. This was dissolved in 25 ml of hot chloroform, decolorized with charcoal, filter and then reprecipitated by addition of petroleum ether, yield 110 mg, m. p. 70-71° C (7.25 percent).

Determination of the carbon dioxide found the permanganate oxidation of 4-Methylpyrimidine

The alkaline solution from the oxidation of six grams of 4-methylpyrimidine was concentrated to exactly 250 ml. A 25 ml aliquot of this concentrate was then titrated with standard 0.1N nitric acid solution using apH meter to measure the changes in hydrogen ion concentration. Aplot of the hydrogen ion concentration versus the amount of 0.1N nitric acid was made from which the bicarbonate ion was estimated.

Figure 3 gives the results in which the yield of pyrimidine-4-

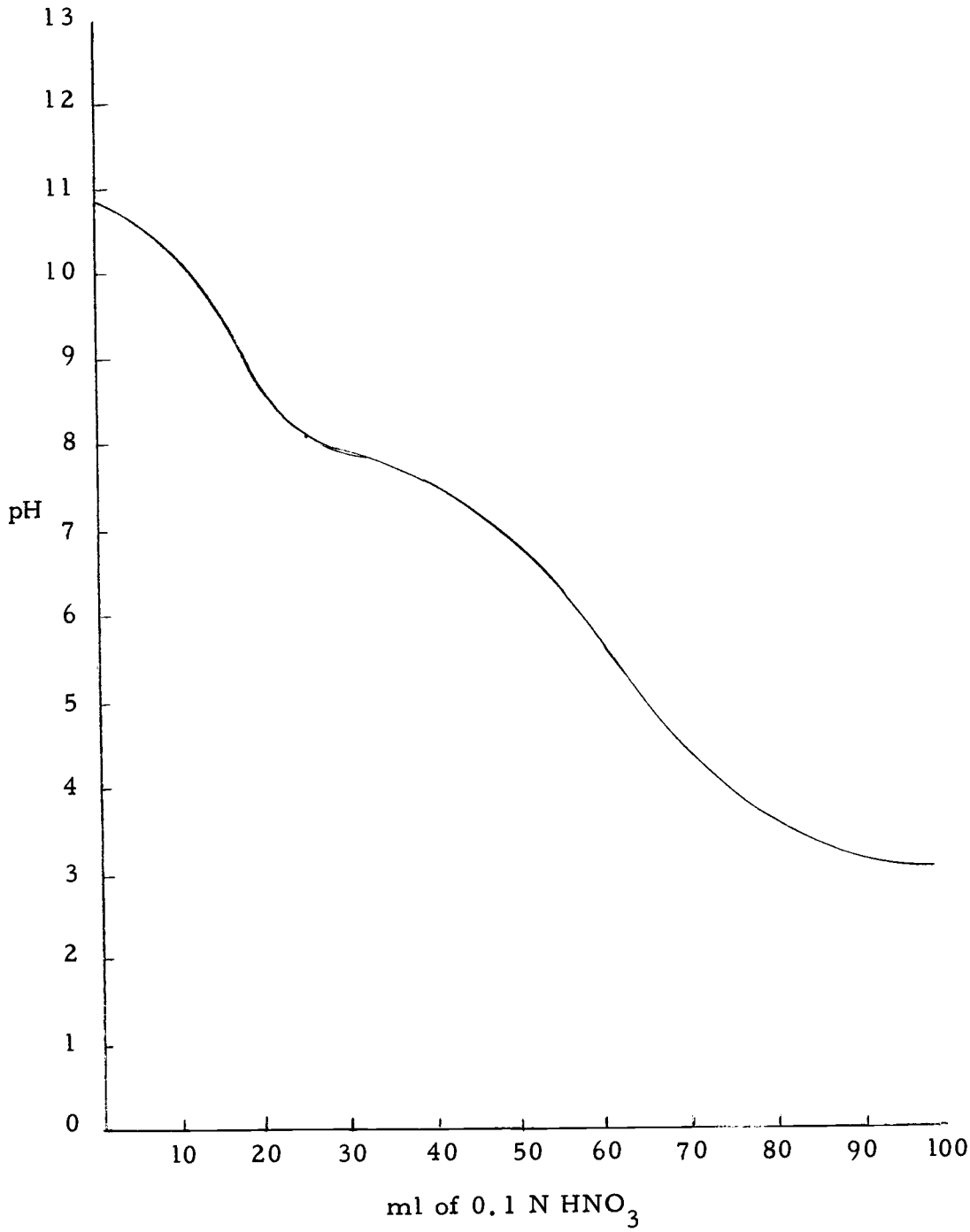


Figure 3. Titration curve: 25 ml aliquot of 250 ml concentrate from oxidation of 4-methylpyrimidine.

carboxylic acid was 25 percent. In this run 0.0047 moles of HCO_3^- was present in 25 ml of concentrate giving a tital yield of 73.5 percent for the run (assuming one mole CO_2 per mole 4-methylpyrimidine consumed).

Figure 4 gives the results for a run in which additional potassium hydroxide was added along with the potassium permanganate. This increased the yield of pyrimidine-4-carboxylic acid to 77 percent, only 23.4 percent of HCO_3^- ion could be accounted in the total concentrate.

	Exp. 1	Exp. 2
ml of 0.1N HNO_3 to neutralize HCO_3^-	47	15
Moles of HCO_3^-/aliquot	.0047	.0015
Moles of 4-methylpyrimidine used/run	.064	.064
% of 4-methylpyrimidine converted to pyrimidine and carbon dioxide	73.5	23.4
Yield of pyrimidine-4-carboxylic acid	25.0	77.0

Determination of ionization constant of pyrimidine-4-carboxylic acid

Several solutions at various pH's including pH 1 and pH 13 were prepared. The spectral transmission curves of these solutions were taken in the ultraviolet. This data is presented in Figure 5.

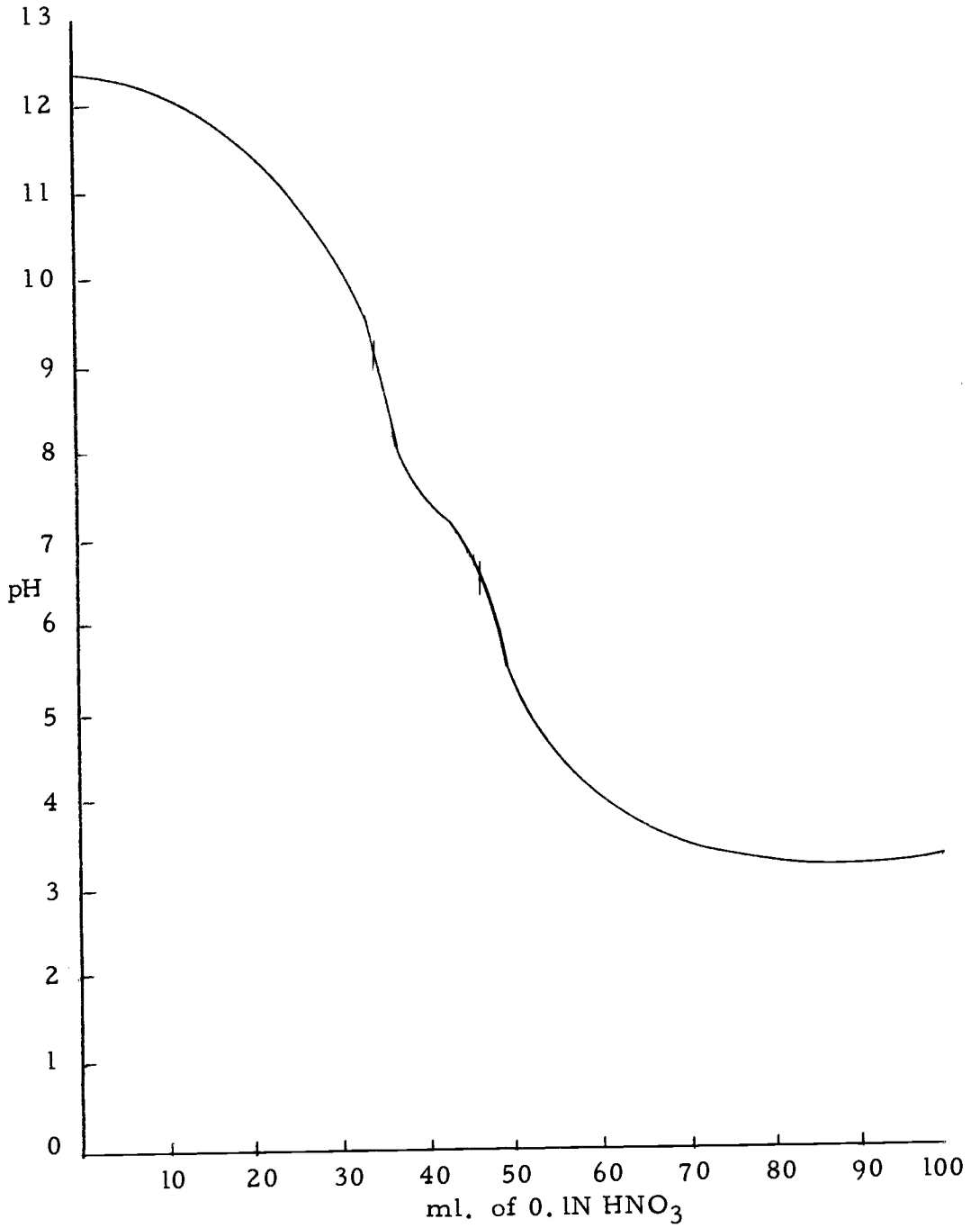


Figure 4. Titration curve : 25 ml aliquot of 250 ml concentrate from oxidation of 6 g of 4-methylpyrimidine, KOH added.

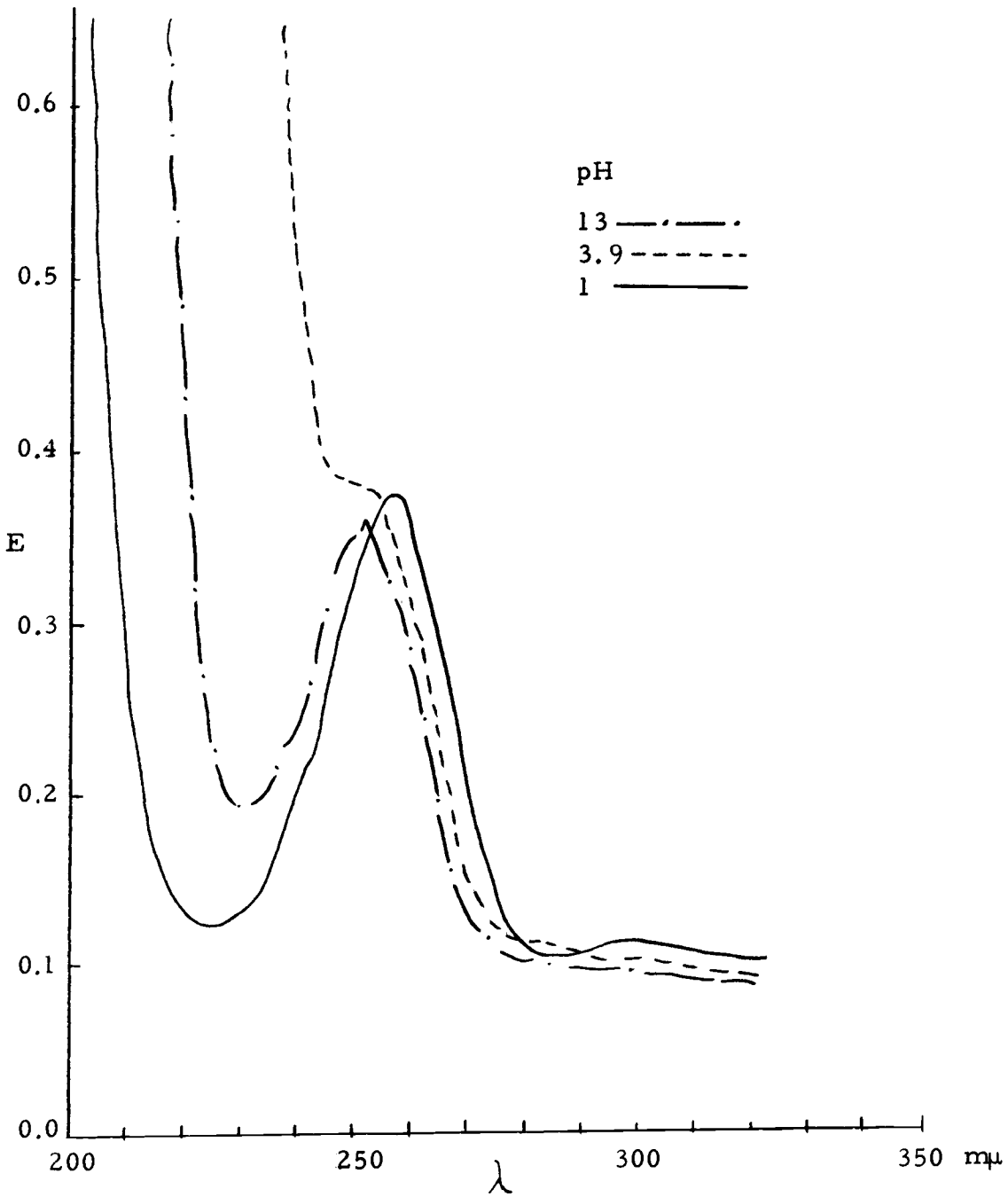


Figure 5. Spectral transmission curves of pyrimidine-4-carboxylic acid at pH 1, 13 and 3.9.

pH	E	Ka
1.0	3160	
13.0	2683	
3.9	2300	6.14×10^{-4}

Determination of the solubility of pyrimidine-4-carboxylic acid in water

One gram of pyrimidine-4-carboxylic acid was suspended in 100 ml of distill water stirred for one hour at room temperature and then filtered. Upon titration with standard 0.1 N sodium hydroxide solution, the acid filtrate was found to be 0.03 N with respect to pyrimidine-4-carboxylic acid.

$$25 \text{ ml acid} \times N = 7.45 \text{ ml} \times 0.1 \text{ N NaOH}$$

From this data it appears that the approximate water solubility of the acid is 3.72 g/liter at room temperature.

SUMMARY

The permanganate oxidation of 4-methylpyrimidine gives low yields (25 percent) of pyrimidine-4-carboxylic acid due to the decarboxylation of some of the acid product.

Pyrimidine has been isolated and identified as one of the products of this oxidation. No unreacted 4-methylpyrimidine survived the reaction as reported by Gabriel (8)

The addition of potassium hydroxide to the reaction mixture of the permanganate oxidation increases the yield of pyrimidine-4-carboxylic acid from 25 to 92 percent. Several derivatives including pyrimidine-4-carbamide and 4-bromacetylpyrimidine have been prepared.

The ionization constant of pyrimidine-4-carboxylic acid has been determined and found to be 6.1×10^{-4}. Pyrimidine-4-carboxylic acid is soluble only to extent of one part in 300 at room temperature but is fairly soluble in hot water from which can be crystallized.

2, 6-Dichloro-4-methylpyrimidine was found to be unstable even at deepfreeze temperatures. It is rendered unless for synthetic purposes by storage over a period of two weeks.

4-Methylpyrimidine is best prepared by the method of Bredereck, Gompper and Morlock (4).

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